CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	August 25, 2011
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	22-150
Proprietary / Established (USAN) Names	Firazyr Icatibant
Dosage Forms / Strength	Subcutaneous injection 30 mg
Proposed Indication(s)	Hereditary angioedema (HAE)
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding icatibant and the reviews in the action package, including my first cycle review, give additional detailed discussion. Icatibant is a synthetic decapeptide competitive antagonist of the bradykinin type 2 (B2) receptor for which Jerini US., Inc. is seeking approval for use in the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older. Icatibant is supplied in a package containing a pre-filled syringe with 30 mg icatibant acetate in 3 mL of solution and a separate sterile needle. The proposed dose of icatibant is 30 mg administered subcutaneously, with the option in cases of insufficient relief or relapse of two additional 30 mg doses administered at intervals of no less than 6 hours. A total of 3 doses in a 24-hour period may be administered.

HAE is a rare disease affecting 1 in 10,000 to 50,000 patients worldwide and is caused by deregulation of the complement cascade. The activity of the first component of complement, C1, is controlled by a serine protease inhibitor C1 inhibitor (C1INH). Patients with HAE have an inherited deficiency (autosomal dominant) of the ability to form C1INH which results in excessive activation of C2 and C4 and the compliment cascade. This excess activation results in the symptoms of HAE which are episodic, localized, recurrent edema of skin, gastrointestinal tract and upper airway. These episodes can be life-threatening, particularly in cases of airway compromise.

The sponsor postulated that a consequence of the uncontrolled activated complement cascade is the uncontrolled release of the vasoactive peptide bradykinin, which is thought to be partially or wholly responsible for the symptoms of HAE. Therefore, icatibant, while not affecting the disease or the cascade pathway itself, was designed to block the product of the cascade pathway (bradykinin) and its biologic effects by competitively blocking the B2 receptor.

Currently, there are two products approved for the treatment of acute attacks of HAE in the US, Berinert and Kalbitor. Both products require administration by a healthcare professional and carry a risk of hypersensitivity reactions, including anaphylaxis. Attenuated androgens and Cinryze are available for prophylaxis.

This cycle of review is of the complete response to the Not Approvable (NA) action that was taken April 23, 2008. The NA action was taken because there was lack of substantial evidence of efficacy to support the proposed indication. At the time of the initial review, the demonstration of efficacy for HAE relied on two small trials utilizing patient reported outcomes (PRO). PROs were used as there are not any objective measures available for disease activity.

The two trials in the original submission were of similar design, except one trial compared icatibant to placebo (FAST-1) and the other trial (FAST-2) compared icatibant to tranexamic acid (TA). The placebo controlled trial failed to demonstrate efficacy, but trended in the correct direction. The trial comparing icatibant to TA did demonstrate statistically significant efficacy, however across trials the time to relief for TA was much longer than that of placebo (12 hours vs. 4.6 hours). This was concerning because while TA is approved in other countries (European Union and South Africa), the review team was unable to find literature that demonstrated adequate trials for the efficacy of TA for acute HAE and some literature reviewed by Dr. Chowdhury seem to indicate that TA may not be effective in acute attacks and perhaps could be harmful. The finding that the time to relief for TA was longer than that of placebo across different trials together with the use of a PRO with which we had little experience made efficacy findings of this trial tenuous. Therefore, one placebo controlled trial did not demonstrate efficacy (but trended in the correct direction), and one TA controlled trial had statistical evidence of efficacy but with several design elements that made interpretation difficult. This did not meet the standard of substantial evidence of efficacy required for approval.

With the initial review, we informed the sponsor that they would need to provide further evidence that icatibant has the purported effect. It was felt that this may be accomplished with one trial instead of two, but the results of the trial would have to be robust as the two existing trials would only be supportive. We also instructed Jerini that they would have to provide data to support self-administration of icatibant by patients, as they were proposing this route of administration. The efficacy deficiencies were explored in a third clinical trial (FAST-3) and the sponsor also provide a self-injection trial (EASSI). FAST-3 demonstrated robust findings of efficacy and EASSI demonstrated that subjects could adequately self-inject. I will discuss this and CDRH's concerns regarding the syringe below.

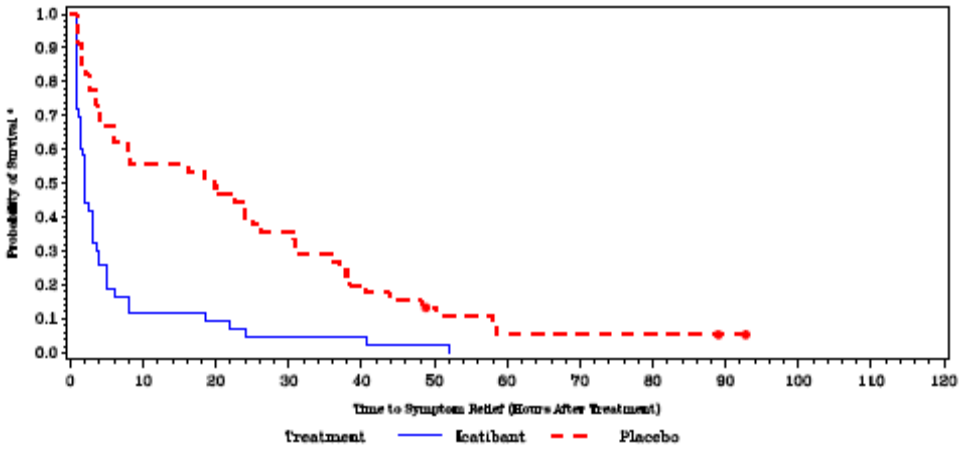
Efficacy

Efficacy is discussed in detail in the excellent reviews of Drs. Porter, Limb and Chowdhury and I refer to those for a detailed description. FAST-3 was a placebo-controlled trial randomizing 223 subjects 1:1 and using a PRO visual analog scale (VAS) to evaluate for efficacy. The VAS utilized a 100 mm horizontal line with 0 mm = no symptoms and 100 mm

= worst possible symptom which subjects used to rate the intensity of each symptom at baseline and at pre-determined time points. Efficacy was assessed using a 3-item composite VAS score, comprised of averaged assessments to skin swelling, skin pain, and abdominal pain. The primary efficacy endpoint was the median time to onset of symptom relief, defined as at least a 50% reduction from the pretreatment composite VAS score. Numerous secondary endpoints were also monitored (i.e. time to relief of the primary presenting symptom, time to relief of each symptom other than the primary symptom, individual symptom severity scoring on a 5-point scale, time to start of symptom improvement, durability of response), some independent of VAS evaluation. Laryngeal attacks were also analyzed but were separate from the primary endpoint and evaluated symptoms of dysphagia, voice change, breathing difficulties, stridor and asphyxia.

FAST-3 demonstrated robust findings with icatibant use compared to placebo with median time to onset of symptom relief of 2.0 hours (95% CI 1.5, 3.0) compared to 19.8 hours (95% CI 6.1, 26.3) respectively. This is represented in the following figure from Dr. Limb's review (figure 2, page 17).

Figure 1 FAST-3: Time to onset of symptom relief based on the 3-symptom composite VAS (VAS-3)



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As with FAST-1 and FAST-2, treatment differences for abdominal attacks were smaller as compared to cutaneous attacks, although both demonstrated statistically significant results. Similar results were demonstrated for the secondary endpoints of single-symptom VAS (table adapted from Table 4, page 18, Dr. Limb's review).

Table 1

FAST-3 Median time to onset of symptom relief (hrs) based on 3-symptom composite VAS					
	Icatibant 30 mg SC		Placebo		P value
	N	Time (h)	N	Time (h)	
All Attacks	43	2.0	42	19.8	<0.001
Cutaneous	26	2.0	23	23.9	0.001
Abdominal	17	1.5	19	4.0	0.003

The time-to-response treatment difference between icatibant and placebo for all attacks was nearly 18 hours and was highly statistically significant. Abdominal attacks in the placebo group appeared to resolve sooner than cutaneous attacks suggesting the natural course of abdominal attacks differs from cutaneous attacks. Secondary endpoints were supportive of icatibant's efficacy and two that are notable include the median time to almost complete symptom relief (all VAS<10 mm) was 8.0 hours compared to 36.0 hours (p=0.012) and rescue medication was used in three of 43 (7%) subjects in the icatibant group (up to 120 hours post-treatment) compared to 18 of 45 (40%) subjects in the placebo group.

In FAST-3, ten subjects presented with laryngeal attacks and were treated with icatibant during the double-blind treatment portion of the trial. Two subjects originally randomized to placebo developed symptoms that were considered severe enough by the investigators to warrant treatment with open-label icatibant and therefore there is not a true placebo group for comparison. However, the median time to onset of symptom relief using the 5-symptom laryngeal VAS composite scoring was 2.5 hours. Also, one of the placebo subjects seemed to be progressing with symptoms after administration of placebo in a blinded fashion, which subsequently resolved after receiving icatibant as rescue medication. Th time to relief is very similar to that of other anatomical sites, shorter than what one might expect from a self-limited attack if there was no effect[1], giving some demonstration of efficacy (although without placebo comparison).

Data from open-label repeat use indicates that icatibant remains effective with intermittent, repeat use.

Safety

The most common adverse reaction is local injection site irritation characterized by erythema and local swelling. These reactions were self-limited and resolved within a few hours of treatment.

EASSI is an ongoing open-label self-administration trial that has approximately 95 subjects enrolled as of April 2011. All subjects are trained in self-administration at enrollment and include those that have previously received icatibant (n=71) and those that were naïve (n=24). The naïve subjects were to present to a clinical site for the treatment of the first attack before receiving icatibant for self-treatment. There have been no reports of device failures and subject VAS scores, physician Global Assessment and subject questionnaires indicate appropriate satisfaction with self-administration. The majority of subjects report ease and a preference for self-administration, and the adverse events do not indicate any issues with device reliability or performance. The frequency and nature of the reported adverse events, including local injection site reactions, are similar to those observed for the injections administered by a healthcare professional. This type of trial is in essence an actual-use trial which is what we request for other medications for patient self-administration, including over-the-counter drugs. These types of trials require the demonstration of the ability of patients to use the product in the actual environment (to the extent possible). This trial demonstrates that

[1] Khan, DA. Hereditary angioedema: historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis. Allergy and Asthma Proceedings 32. 1 (Jan 2011):1-10

patients can adequately self-inject icatibant for perceived attacks. It should not be too surprising that patients can accomplish this as there are many other disease and medications where patients self-inject (e.g., diabetes, anticoagulants) and many require a more complicated injection regiment than icatibant (i.e., drawing up the medication, altered dosing etc.). In terms of efficacy and patient safety, it would be much preferable to have a medication that can be self-administered because the sooner the attack is treated, the greater the success at abortion of symptoms. Additionally, since HAE is rare, many clinicians do not have the expertise to manage acute attacks, many health care facilities do not stock the appropriate medications, and self-injection allows the patient greater control over appropriate therapy. Self-injection by itself, if the medication is successful, could be viewed as an important advancement over the current armamentarium of therapies that require health-care professional administration. Additionally, icatibant to date has not demonstrated anaphylactic reactions as have other approved medication used in acute HAE attacks, which is also an important safety consideration in any risk:balance analysis.

Our colleagues at CDRH have raised two concerns that they feel should delay the approval of the current package:

1) The pre-filled syringe (b) (4) does not meet ISO standards and therefore may not be compatible with needles outside of those supplied within the pre-packaged kit. The needle (b) (4) Luer lock) within the kit does comply with ISO standards. The (b) (4) Syringe has been approved for use with other products within CDER.
2) Icatibant use for self-injection has not undergone Human Factors testing. While there is abundant clinical data demonstrating adequate safety and efficacy of self-injection, CDRH maintains that type of testing is not intended to identify use related risks that are typically identified/verified/validated during a Human Factors study.

The CDER Chemistry, Manufacturing and Control (CMC) reviewers do not agree with #1 above. They contend that this syringe has been approved with other products and while there have been reports of incompatibility with other commercially marketed medical equipment (e.g., needle-less connectors, needles and IV tubing---mainly with two drug compounds out of the large number of NDA/BLA applications), all bench-testing performed has indicated that the (b) (4) Needle (Luer lock) supplied in the kit is compatible with the (b) (4) Syringe and demonstrated interoperability. Bench testing and syringe needle compatibility testing, while performed in less than the 30 devices (for each of six tests) requested by CDRH, was found supportive of the syringe/needle configuration. This was also supported by the clinical trials (2,044 injections) and world-wide marketing (b) (4) of the same syringe/needle combination where there have not been worrisome reports of device failures. With this level of evidence ONDQA is recommending approval. I agree with their evaluation and recommendation. Of note, further bench testing will be performed, but will be requested of (b) (4) in their Drug Master File (b) (4) as this encompasses a wider scope of issues.

CDRH recommends that Human Factors testing should be performed to demonstrate that icatibant in pre-filled syringes can be self-administered safely and effectively by patients and not a clinical professional. The CDRH consultants state that the purpose of the study is to

demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. If this is the goal of the testing, one could posit that Human Factors testing should be performed prior to actual field testing to be hypothesis generating regarding potential safety problems that may be remediated prior to field testing. In this instance, we have abundant data indicating success with self-injection. To follow CDRH's recommendation seems counter-intuitive, as we have a great deal of actual use, by HAE patients, under real use conditions, and there have not been any patterns of failures emerging with self-administration that need remediation. Therefore, I do not agree that a Human Factors study is relevant or necessary in this situation and believe that the delay in marketing while one is being performed would actually be detrimental to the health of those patients with HAE that do not have ready access to treatment at a center with expertise in this disease. I also believe that the demonstration of adequate self-use within a clinical trial is consistent with how we have evaluated other medications where a device is involved. It should not be lost that as patient self-injections go, this is one of the simpler programs that we have, particularly when compared to insulin therapy where doses changes and different types of insulin may be mixed within the same syringe, or other drugs where reconstitution is required. I also note that CDRH requests 15 participants from each major user group for validation, but far more than that have been studied in the trial referenced above.

While I agree with CDRH that critical assessment should be performed on device compatibility and use, I believe that adequate testing has been performed for this product.

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on June 23, 2011. The panel voted 12 yes, 1 no that the data supported approval for marketing of icatibant. Most comments reflected this voting. Panel members voiced and voted strong support for self-administration and believed this was an important benefit of icatibant use.

2. Conclusions and Recommendations

Icatibant has demonstrated appropriate efficacy and safety in the treatment of HAE to allow marketing and will be a valuable addition to the armamentarium of patients with this disorder and should be made available without any delay.

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/s/

CURTIS J ROSEBRAUGH
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